

Practical recommendations for timely, accurate diagnosis of symptomatic Alzheimer's disease (MCI and dementia) in primary care: a review and synthesis

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Abstract. Liss JL, Seleri Assunção S, Cummings J, Atri A, Geldmacher DS, Candela SF, Devanand DP, Fillit HM, Susman J, Mintzer J, Bittner T, Brunton SA, Kerwin DR, Jackson WC, Small GW, Grossberg GT, Clevenger CK, Cotter V, Stefanacci R, Wise-Brown A, Sabbagh MN (The Columbus Memory Center, Columbus, GA; Medical Affairs – Neuroscience, Genentech, A Member of the Roche Group, South San Francisco, CA; University of Nevada, Las Vegas, NV; Lou Ruvo Center for Brain Health – Cleveland Clinic Nevada, Las Vegas, NV; Banner Sun Health Research Institute, Sun City, AZ; Brigham and Women's Hospital, Boston, MA; Harvard Medical School, Boston, MA; University of Alabama at Birmingham, Birmingham, AL; Health & Wellness Partners, LLC, Upper Saddle River, NJ; New York State Psychiatric Institute and Columbia University Irving Medical Center, New York, NY; Icahn School of Medicine and Mt. Sinai, New York, NY; Alzheimer's Drug Discovery Foundation, New York, NY; Northeast Ohio Medical University, Rootstown, OH; Roper St Francis Healthcare, Charleston, SC; Ralph H. Johnson VA Medical Center, Charleston, SC, USA; F.Hoffmann-LaRoche, Basel, Switzerland; Touro University, Vallejo, CA; Kerwin Medical Center, Dallas, TX; University of Texas Southwestern Medical Center, Dallas, TX; University of Tennessee College of Medicine, Memphis, TN; University of California – Los Angeles, Los Angeles, CA; St Louis

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The critical role of primary care clinicians (PCCs) in Alzheimer's disease (AD) prevention, diagnosis and management must evolve as new treatment paradigms and disease-modifying therapies (DMTs) emerge. Our understanding of AD has grown substantially: no longer conceptualized as a late-in-life syndrome of cognitive and functional impairments, we now recognize that AD pathology builds silently for decades before cognitive impairment is detectable. Clinically, AD first manifests subtly as mild cognitive impairment (MCI) due to AD before progressing to dementia. Emerging optimism for improved outcomes in AD stems from a focus on preventive interventions in midlife and timely, biomarker-confirmed diagnosis at early signs of cognitive deficits (i.e. MCI due to AD and mild AD dementia). A timely AD diagnosis is particularly important for optimizing patient care and enabling

the appropriate use of anticipated DMTs. An accelerating challenge for PCCs and AD specialists will be to respond to innovations in diagnostics and therapy for AD in a system that is not currently well positioned to do so. To overcome these challenges, PCCs and AD specialists must collaborate closely to navigate and optimize dynamically evolving AD care in the face of new opportunities. In the spirit of this collaboration, we summarize here some prominent and influential models that inform our current

understanding of AD. We also advocate for timely and accurate (i.e. biomarker-defined) diagnosis of early AD. In doing so, we consider evolving issues related to prevention, detecting emerging cognitive impairment and the role of biomarkers in the clinic.

Keywords: Alzheimer disease, biomarkers, dementia, disease-modifying therapies, mild cognitive impairment, primary health care.

Introduction

The primary care setting is often a patient's entry point into the healthcare system [1], and primary care clinicians (PCCs) emphasize first-contact accessibility and accountability for the whole person and integration, continuity, comprehensiveness and coordination of services [1, 2]. As a result, PCCs are critical to the management of complex and chronic diseases such as Alzheimer's disease (AD) dementia, and they are intimately involved in AD dementia prevention, diagnosis and care [3]. In a recent Alzheimer's Association Primary Care Physician Dementia Care Training Survey, 82% of PCCs reported being on the front lines of providing critical elements of dementia care [4]. The vast majority of PCCs (93%) felt that it was their duty to stay informed on current and new developments in AD care management, including screening, diagnosis, treatment and monitoring. Despite this, half of PCCs (53%) reported the extent to which they keep up with new developments in dementia care as 'only a little' or 'not at all', reflecting, at least in part, the enormous demands on their time and energy across all health-related domains [4]. A sizeable proportion of these clinicians noted that they are 'never' or only 'sometimes' comfortable making a diagnosis of AD dementia (39%), whilst more than half (55%) acknowledged that local specialist resources are insufficient to meet patient demand [4].

These challenges are reflected clearly in clinical practice, as studies suggest that many cases of AD dementia go unrecognized and undiagnosed for years after symptom onset [5, 6]. Even when dementia is diagnosed, a specific aetiology is not assigned in the vast majority of cases [7]. Most patients who receive a specific diagnosis of AD dementia are unfortunately diagnosed when they have already progressed to the moderate or severe stages of disease – stages at which even basic activities of daily living (ADLs) generally are compromised and

substantial independence has already been lost [8]. Missed and delayed diagnoses reflect a multitude of gaps in knowledge along with other complex factors [9, 10], including the mistaken belief that memory loss and other cognitive problems are a normal part of ageing; denial or lack of recognition amongst patients, caregivers and clinicians; and the absence of reliable, accurate and simple AD biomarkers [9, 10]. Finally, the erroneous belief that the consequences of avoiding a diagnosis for the patient and family are negligible further perpetuates the norm of delayed or missed diagnoses.

Significant progress has been made in the development of disease-modifying therapies (DMTs) for AD, and the first drug may be available to patients as early as 2021 [11]. It is critical to note that most current AD DMT studies are conducted in patients who are in the earlier stages of AD (i.e. prodromal diseases such as mild cognitive impairment due to AD, mild AD dementia and, increasingly, even preclinical populations) and that patients included in these studies have had AD pathology confirmed objectively via biomarker measurements. These factors have significant implications for clinical practice, given that most patients are diagnosed late in their disease and clinical course, and AD diagnosis rarely includes biomarkers of AD pathology. Moreover, healthcare systems worldwide, including in the United States, are not fully prepared to handle the expected caseload when AD DMTs become available [12]. Modelling of current United States healthcare capacity suggests that patients would have to wait an average of 18.6 months for treatment after introduction of a DMT for AD. This delay would result in approximately 2.1 million patients progressing to AD dementia whilst waiting for treatment during the first 2 decades after an AD DMT is first available. The most significant constraint on projected patient care is the limited capacity of expert clinicians to evaluate and diagnose patients.

Primary care clinicians are expected to play a major role in overcoming these challenges, as they are optimally positioned to detect the earliest signs and symptoms of cognitive impairment/dementia [3]. For example, recent analyses suggest that triaging patients at the primary care level based on the use of an objective cognition-screening tool along with in-development blood-based biomarkers (BBBMs) represents a potentially efficient and cost-effective path to accurately identifying incipient AD-related cognitive decline earlier in the disease course. Such a strategy could eliminate waiting lists for DMT treatment after the first 3 years, whilst increasing correctly identified cases by 120 000 annually [13]. If the healthcare community is to rise to the challenge, embracing fresh perspectives and new paradigms regarding the diagnosis and treatment of AD, a coordinated effort amongst the multidisciplinary healthcare professional team, policymakers, patient advocates and payers is critical.

In this review, we advocate for more consistent, reliable and timely detection of AD, particularly mild cognitive impairment (MCI) and mild AD dementia. Such early detection may enable practitioners to intervene and attempt to delay functional decline and disability. In addition, we highlight the main research models and data that support the goal of timely diagnosis, review the anticipated benefits of such a shift in diagnostic patterns, provide guidance on detecting and evaluating patients presenting with cognitive concerns and discuss the role of current and emerging biomarkers in facilitating more timely and accurate diagnosis. We hope to foster ongoing dialogue between the primary care community and AD specialists, as such communication will not only be essential to maximizing AD management today, but also in navigating the healthcare landscape that will emerge in the years ahead. We also present scientific and medical advances in a context that is pragmatic and relevant to – and even readily implementable in – the primary care setting.

Reconceptualizing Alzheimer's disease as a dynamic, long-term pathophysiological–clinical continuum with objective markers

Advances in the AD field have led to a reconceptualization of the disease, moving our understanding beyond the dementia-focused clinical presentation of AD to a construct that includes early pathophysiological changes in asymptomatic individuals. In this section, we will summarize the journey of individuals along the pathophysiological–clinical

AD continuum, illustrated by a well-known biomarker model of AD [14, 15], and by two prominent AD classification systems [16–21].

Biomarker model brings objectivity to the conceptualization of AD

In 2010, Jack et al introduced a hypothetical biomarker model that aimed to amalgamate the contemporary knowledge on AD pathology with the then-emerging concept of the AD continuum [14]. This model, depicted in Fig. 1a, is predicated on AD pathology developing over decades and suggests that AD biomarkers evolve in a predictable and sequential yet temporally overlapping manner. The model also acknowledged that AD pathology is present even in the absence of symptoms and that gradual cognitive and functional impairments are observed as the disease pathology progresses [14, 22]. Besides incorporating the two hallmarks of AD pathology – accumulation of amyloid-beta ($A\beta$) and tau protein (Box 1), this model also includes biomarkers of neurodegeneration. In general, $A\beta$ biomarkers are largely state biomarkers, reflecting disease presence, whereas different tau biomarkers can reflect either state (i.e. disease presence) or stage (i.e. disease progression). Neurodegeneration biomarkers are largely stage markers, progressing in close concordance with clinical symptoms [23].

New diagnostic systems link disease presentation to objective assessments of AD pathology

There are two main classification schemes for the AD continuum: the US National Institute on Aging–Alzheimer's Association Classification (NIA-AA; Fig. 1b) [16–18], and the International Working Group Classification (IWG) [19–21]. These frameworks facilitate standardization in the research setting and enable didactic exchanges (Table 1) [24–26]. These models also allow for an AD diagnosis based not solely on appreciable symptoms, but also on the measurement of AD pathology markers [27, 28]. Evaluation of these biomarkers can help to distinguish MCI due to AD from cognitive impairment due to other conditions, especially in the earlier stages of disease [103].

Phases of AD across the lifespan

The preclinical (asymptomatic) phase

The accumulation of $A\beta$ peptides in the AD brain results from complex interactions between numerous genetic and environmental factors [30–33]. This accumulation, which reflects an imbalance

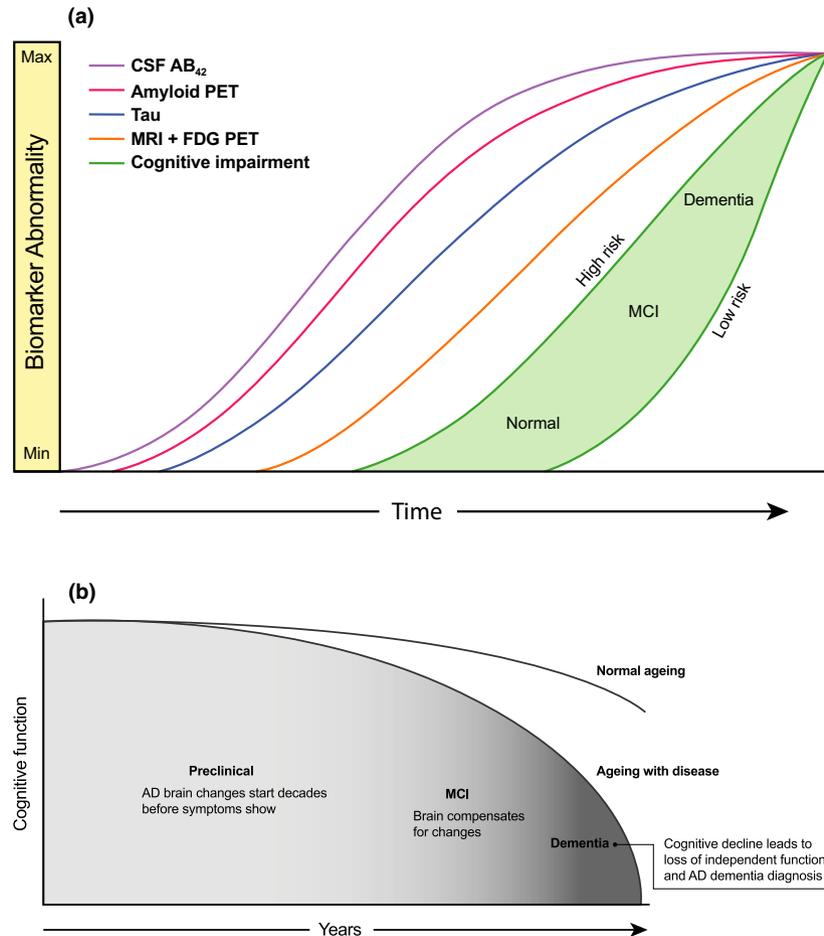


Fig. 1 (a) Dynamic biomarkers of the AD pathological cascade model. (b) Hypothetical model of the pathologic-clinical continuum of AD. AB, amyloid-beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography. (a) reprinted from The Lancet Neurology, Vol. 12, Jack CR Jr et al, Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers, 207–216, ©2013, with permission from Elsevier [15]. (b) adapted from Sperling et al. [16]

Box 1. The amyloid and tau hypotheses in AD

The amyloid hypothesis suggests that the accumulation of A β in the brain, which results from an imbalance between production and clearance of A β peptides, is an early initiating factor in AD that is present during the asymptomatic stage of the disease [36].

The tau hypothesis suggests that AD progresses primarily through tau pathology that is either independent of, or codependent with, A β accumulation [194]; one perspective on the biology of AD is that it is an amyloid-facilitated tauopathy. Studies in AD have demonstrated that the density of tau pathology in the brain correlates strongly with neuronal dysfunction and neurodegeneration [195,196]. Pathological tau may propagate from cell to cell, in a prion-like manner, via the extracellular space. In AD, this cell-to-cell propagation can occur in a characteristic spatiotemporal pattern throughout the brain, coinciding with clinical burden and disease progression [196,198].

Abbreviations. A β , amyloid-beta; AD, Alzheimer's disease.

Adapted from Livingston et al, Lancet 2020; 396:413-46 [103].

Table 1 Key similarities and differences in IWG-2 and NIA-AA diagnostic criteria for Alzheimer's disease

Similarities	
<ul style="list-style-type: none"> • Incorporate certain biomarkers (e.g. increased Aβ on PET; decreased CSF Aβ 1-42; increased CSF t-tau or p-tau; decreased hippocampal volume) into the diagnostic process • Conceptualize disease biology as beginning before symptoms appear • Move towards an aetiological diagnosis for MCI • Recognize three basic stages of AD <ul style="list-style-type: none"> – Asymptomatic/presymptomatic phase with biomarker evidence of AD pathology – Symptomatic, predementia phase of AD – AD dementia phase 	
Differences	
IWG-2	NIA-AA
Asymptomatic at risk	Preclinical AD
Prodromal AD	MCI due to AD
'AD' refers only to symptomatic stage; 'Alzheimer's pathology' refers to disease pathology at any stage	'AD' refers to the pathologic process, whether individual is asymptomatic or symptomatic
Requires objective impairment in memory (impairment in other cognitive domains may also be present, but is not required for diagnosis)	Requires measurable impairment in any cognitive domain
Biomarker abnormalities required for diagnosis	Biomarker abnormalities support diagnosis, but are not required for symptomatic phases of disease

Abbreviations: A β , amyloid- β ; AD, Alzheimer's disease; CSF, cerebrospinal fluid; IWG, International Working Group; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging-Alzheimer's Association; PET, positron emission tomography.

Table modified from Morris et al. [169].

between production and clearance of A β peptides [34–36], starts as early as 25 to 30 years before symptoms arise [15, 34–41]. Two concepts were introduced to describe this phase in the AD continuum: preclinical AD [16] and asymptomatic at risk of AD [20]. Both of these designations reflect a recognition that AD starts before the occurrence of clinical symptoms, but the terms also connote subtle conceptual differences; most prominently, 'preclinical' AD suggests the diagnosis of AD in

asymptomatic individuals who have biomarker evidence of A β accumulation [16], whereas the 'asymptomatic' label reflects an 'at-risk' stage that is not yet considered to be the disease itself (Table 1).

The first measurable evidence of AD is abnormally reduced levels of A β 1-42 in the cerebrospinal fluid (CSF), which results from more A β being sequestered in the brain parenchyma [34, 35, 42]; this is

followed by increased A β tracer retention observed in positron emission tomography (PET) scans (directly reflecting A β build-up) [42]. Subsequent to these changes, elevated concentrations of fluid biomarkers directly associated with neuronal injury/death (e.g. t-tau, p-tau181, VILIP-1 and neurogranin) are observed [34, 35]. Evidence of neurodegeneration can also be observed in functional neuroimaging modalities, such as fluorodeoxyglucose PET, in which glucose hypometabolism is observed in the parietal and temporal regions of the brain. Structural neuroimaging techniques such as volumetric magnetic resonance imaging (MRI) may also show hippocampal and entorhinal cortex atrophy and cortical thinning during this phase [35, 43]. Like A β biomarkers, these markers can be identified in individuals at risk of AD several decades before the onset of cognitive deficits [38], although individual variability in brain structure lowers their predictive utility.

The accumulation of A β is associated with an increased risk of developing cognitive decline [33, 43–45] and progression towards symptomatic AD [33, 43]. Although all patients with AD demonstrate abnormal A β accumulation, that accumulation alone is not sufficient to lead to the clinical presentation of AD [41, 43, 46]. In fact, some individuals with A β pathology may never convert to symptomatic phases of AD during their lifetime [16]. In contrast, the presence of a second elevated marker of either tau pathology or neurodegeneration in an individual demonstrating excess A β accumulation (i.e. one who is positive on an A β biomarker) is associated with greater prognostic predictability, reflected clinically by a more consistent and rapid progression [33, 41, 47].

In summary, during the preclinical phase of AD, A β deposition is followed by a sequence of events, including tauopathy and abnormalities in markers associated with synaptic dysfunction and neuronal death, all of which occur before the onset of cognitive and functional impairments [35]. These data open the possibility for a biomarker-based AD diagnosis at a disease stage where interventions could be introduced to potentially slow, or even stop, the emergence of symptoms.

Mild cognitive impairment due to AD

Mild cognitive impairment due to AD marks the beginning of the symptomatic stage of the disease. From a biomarker perspective, patients in this

phase experience a deceleration or even a plateau in A β accumulation [16, 22, 39]. Both tau accumulation and further neurodegeneration, including impaired glucose metabolism and hippocampal atrophy, continue throughout clinical expression of disease and are more tightly correlated with and predictive of the degree of cognitive impairment a person will experience [35, 48]. The effects of AD pathology on cognitive and other clinical manifestations are gradual and progressive, making it presently impossible to define a discrete onset of the clinical state [47]. Eventually, as AD pathology progresses, individuals begin to exhibit subtle cognitive deficits, entering a transitional phase of MCI due to AD, also known as prodromal AD. Although these terms are interchangeable, in this review we will use the term MCI due to AD.

Clinical criteria for a diagnosis of MCI include concern regarding a decline in cognition coupled with objective evidence of impairment in one or more cognitive domains, a preservation of independence in functional abilities and no evidence of significant impairment in social or occupational functioning (as would be seen with dementia) [17]. When patients begin to display signs of MCI due to AD, memory and executive function are often, but not always, the main cognitive domains affected, and patients begin to experience difficulty performing instrumental activities of daily living (IADLs) – for example shopping, following complex cooking recipes, and handling finances [26, 49–51]. In addition, somewhere between 35% and 85% of patients with MCI exhibit at least one neuropsychiatric symptom, most commonly depression, irritability, apathy, anxiety, agitation and sleep problems [52]. These symptoms may serve as additional diagnostic clues, and research suggests that some of these symptoms may help predict further disease progression and decline along the AD continuum [52].

Between 30% and 50% of patients with MCI will convert to AD dementia over a 5- to 10-year period [53, 54], and amnesic MCI is the subtype of mild impairment most consistently predictive of such progression [17]. Studies analysing the progression from the broad category of MCI (due to any reason) to AD dementia have reported annualized conversion rates ranging from approximately 8–17% for clinical samples (i.e. those enrolled from memory clinics) and 5–12% for community samples [53]. The likelihood of progression from MCI to AD dementia is influenced by a number of risk factors,

some of which are potentially modifiable (e.g. cardiovascular disease, metabolic syndrome, psychiatric illness, use of psychoactive drugs) and others that are not modifiable (e.g. presence of at least one allele of the apolipoprotein e4 gene) [55].

Dementia due to Alzheimer's disease

For most patients, when MCI results from AD pathology, it is followed by AD dementia, which is a relatively late stage of disease compared with the initial accumulation of A β . AD dementia is a stage at which A β distribution in the brain is at its most pronounced, tau accumulation advances to its maximum, and neurodegeneration continues and becomes more macroscopically evident. Medial temporal atrophy affecting the amygdala and hippocampus, usually accompanied by enlargement of the temporal horn, is typical of AD. Other features suggestive of AD include moderate cortical atrophy, most evident in multimodal association between cortices and limbic lobe structures, and enlarged sulcal spaces with atrophy of the gyri in frontal and temporal cortices [56].

Further deterioration in memory and executive function, as well as the emergence of impairment in other cognitive domains (e.g. visuospatial skills and language), prevent individuals from performing not only IADLs, but even basic ADLs (e.g. bathing, grooming and eating) [26, 50, 51, 57]. Neuropsychiatric symptoms (e.g. apathy, psychosis, mood disorders and agitation) are common, especially in moderate and severe stages of disease [58]. These symptoms are usually associated with significant disruption to the household or caregiving unit, and are a key cause of institutionalization [59–63]. Both patients with AD dementia and their caregivers are likely to experience diminished quality of life due to psychological and humanistic suffering, financial strain, inability to carry out normal activities and general stress on the family [64].

Other causes of MCI and dementia

On their own, the terms 'MCI' and 'dementia' do not indicate a particular aetiology. Instead, they may result from vascular disease, Parkinson's disease or Lewy body accumulation, major depressive disorder, sleep disorders, substance abuse, polypharmacy, other aetiologies or a combination of aetiologies – instead of, or in addition to, AD neuropathologic changes [65, 66]. The heterogeneity of MCI is a major challenge to timely diagnosis

of MCI due to AD. Characterizing the nature and then accurately diagnosing the aetiology of any observed cognitive and behavioural impairment are paramount, as some may be correctable (e.g. polypharmacy, major depressive disorder, sleep disorders) but others are not. In addition, cognitive impairments of differing aetiologies require different treatments and care strategies, and are associated with differing prognoses [59]. Pathology in dementia often overlaps: for example, vascular dementia – such as multi-infarct dementia or subcortical vascular encephalopathy – is the most common concurrent pathology in a patient with AD pathology [56, 67]. Because AD is rarely found without other neurodegenerative co-pathologies [56, 67], a physician should not let evidence of one dementia type preclude their assessment for other pathologies such as AD. Forthcoming DMTs for AD will apply specifically to AD-related MCI and dementia, underscoring the importance of biomarker confirmation in diagnosis of AD.

The importance of timely diagnosis of AD

One goal of 'timely diagnosis' of emerging cognitive impairment is to preserve as much independence for a patient, for as long as possible. Thus, timely diagnosis of AD refers to diagnosis at a stage when individuals can come to the attention of clinicians because of concerns about changes in cognition, behaviour or functioning, but whilst they are still relatively functionally independent [10]. Timely diagnosis of AD is a product of a case-finding approach that often requires the use of decision-support tools to detect 'at-risk' individuals [68, 69]. Such case finding necessarily includes patient-centred clinical judgement about whether offering an evaluation of cognitive impairment/dementia is appropriate, because it may lead to indicated medical interventions [70]. 'Timely' diagnosis of AD can be contrasted with the idea of 'early' diagnosis, with the latter enabled by mass population screening (e.g. for nonreported cognitive decline or the presence of an AD biomarker) [69]. A timely diagnosis of AD, however, implies shifting recognition and diagnosis of the disease from the moderate and severe stages of dementia to earlier disease periods – that is, during the stages of mild AD dementia or even MCI due to AD.

In a medical context, vigilance and active inquiry for emerging cognitive impairment symptoms should be high [71]. Multiple professional societies recommend the timely diagnosis and management

of AD, including the Centers for Medicare & Medicaid Services, which offers reimbursement for a cognitive function assessment as part of the Medicare Annual Wellness Visit [72]. In their 2018 MCI practice guidelines, the American Academy of Neurology (AAN) stresses the importance of MCI detection [73], and Alzheimer's Association outlines a practical approach to timely diagnosis and disclosure, in an effort to reduce the number of patients experiencing delayed diagnosis [74, 75]. The UK National Institute for Health and Care Excellence (NICE) guidelines recommend early and

ongoing discussions of dementia management with patients and their caregivers [76]. Timely recognition of cognitive impairment and timely diagnosis of AD translate into a number of benefits for patients and their caregivers (Box 2).

Timely diagnosis in the context of pharmacological intervention

At present, cholinesterase inhibitors and an N-methyl-D-aspartate (NMDA) receptor antagonist are commercially available to treat patients with AD dementia. None of these, however, are disease-

Box 2. Benefits of timely recognition and diagnosis of cognitive impairment

- Prompts early evaluation for common, treatable and potentially reversible causes of cognitive impairment, which may include the following:
 - a Major depressive disorder, anxiety, vitamin deficiency, sleep disturbances, hearing or vision loss, metabolic disorders, pain syndromes, substance abuse/dependence (including alcohol), sleep apnoea and side effects from medication (e.g. anticholinergics, benzodiazepines, sedative-hypnotics, narcotics, antipsychotics, antidepressants and antiepileptics)
- Enables patient and family education and counselling about existence and implications of a diagnosed illness, which may help mitigate the following:
 - a Family and marital discord
 - b Risk of home and community mishaps such as house fires, motor vehicle collisions, wandering and weapons access
 - c Legal and law enforcement encounters
 - d Caregiver burden
 - e The likelihood of financial fraud or other exploitation of the patient
- Maximizes the time available for medical and estate planning, including creation of support systems, the establishment of a comprehensive medical plan and the development of advance directives
- Allows early introduction of strategies and tools to maximize independence (e.g. daily memory planners; safety bracelets; and electronic technologies such as pill dispensers, GPS pendants, in-home cameras and cloud-based voice/virtual assistant reminders such as Alexa and Siri)
- Enables potential pharmacologic and nonpharmacologic intervention for memory loss, mood and anxiety disorders, and psychosis
- Extends opportunity to control comorbidities that may contribute to cognitive decline and modify lifestyle risk factors (e.g. smoking, exercise, diet) that may slow or mitigate risk of further decline
- Affords opportunity to connect with support agencies, such as Alzheimer's Association (in the case of AD diagnosis), and to enrol in free safety programmes such as "Safe Return"
- Provides more opportunities to participate in clinical research trials
- Consistent with promoting autonomy, justice and beneficence
- May delay nursing home admission

Abbreviation. AD, Alzheimer's disease.

Elements of this table are based upon previously published reports [9,81,124,199–204].

modifying, and no medication has been approved by the US Food and Drug Administration to treat MCI [77–81].

Data suggest that cholinesterase inhibitors may mitigate clinical decline when initiated during the AD dementia stage and maintained through late clinical stages [82–84]. Combination therapy (a cholinesterase inhibitor plus the NMDA antagonist) in patients with moderate-to-severe AD dementia provides cumulative, additive benefits over monotherapy [85–87]. However, these symptomatic therapies do not alter the underlying disease process – they do not interrupt the biological cascades that lead to neuronal dysfunction and loss [88–90]. All patients with AD, including those who are appropriately treated, continue to experience decline over time [88–90]. Failing to appreciate the benefits of available drugs against the backdrop of an inevitably progressive disease may contribute to therapeutic nihilism [91, 92] and may increase the tendency to deprioritize the identification of cognitive impairment [93]. Although patients benefit from these medications, there is little doubt that additional pharmacological interventions that slow or halt the progression of disease are urgently needed [94].

Disease-modifying therapies are defined by their ability to alter a disease course and to provide benefits that, compared with no DMT treatment, grow larger over time. DMT effects in AD, thus, might include an arrest of the disease process or deceleration of the rate of progressive clinical decline [95]. Timely intervention with AD DMTs may offer long-term benefit similar to those observed with early interventions in cancer, cardiovascular disease, stroke, HIV/AIDS and diabetes [43]. Development efforts suggest that DMTs will be most beneficial in early, biomarker-confirmed AD – before significant neuronal damage has occurred [96–98].

Towards timeliness and accuracy: pragmatic aspects of clinical care informed by developing models of AD

Primary care clinicians and AD specialists already collaborate to care for individuals with AD. This partnership will need to evolve when DMTs become available, particularly as new care models are likely to emerge. PCCs will remain on the front lines of AD diagnosis, but new care models may necessitate identifying the signs and symptoms of cognitive-behavioural impairment and making a

clinical diagnosis as early as possible. Several questions remain, however, on the next steps of the patient journey. For example, what is the role of the PCC, and who in the multidisciplinary AD care team will be responsible for the confirmatory diagnosis of AD? Specifically, who will request biomarkers of AD pathology necessary to enable treatment? Who will initiate DMTs and monitor the efficacy and safety of those DMTs?

Although we anticipate that the emergence of an AD DMT will serve as a catalyst for many of these changes, certain collaborative actions between PCCs and AD specialists can be implemented now that will place the healthcare system in a better position to address the needs of individuals with AD when DMTs become available.

Lifestyle interventions can help delay or prevent cognitive decline

Growing evidence suggests that lifestyle interventions may be beneficial not only for cognitively normal individuals at risk of MCI/dementia, but also for people already experiencing symptoms. For cognitively normal individuals at risk, epidemiologic research indicates that one-third to one-half of dementia cases may be attributable to modifiable risk factors and may therefore be preventable [99–103] with improvements in education, exercise, cognitive stimulation, nutrition, health care and reduced tobacco use, along with reductions in or better control of vascular risk factors [66, 103–112]. An emphasis on preventive care is a defining feature of primary care, already well established in everyday clinical practice [3, 113].

Individuals with emerging cognitive impairment may also continue to benefit from lifestyle changes. Both aerobic exercise and resistance exercise appear to improve global cognition, executive function, attention and delayed recall in patients with MCI [114, 115]. Current AAN MCI management guidelines recommend exercise for patients with MCI, noting that exercise training for 6 months is likely to improve cognitive measures in this population [81]. Cognitive training also appears to have beneficial effects on cognitive and psychosocial measures in this patient population [116, 117]. Modest evidence indicates that treatment of major depressive disorder in patients with MCI may slow the pace of cognitive deterioration [115].

A 2020 Lancet Commission provided recommendations for modifying dementia risk across the life

Box 3. Specific actions for risk factors across the life course

- Aim to maintain systolic blood pressure of 130 mm Hg or less in midlife from around 40 years (antihypertensive treatment for hypertension is the only known effective preventative medication for dementia)
- Encourage use of hearing aids for hearing loss; reduce hearing loss by protecting ears from excessive noise exposure
- Reduce exposure to air pollution and second-hand tobacco smoke
- Prevent head injury
- Limit alcohol use
- Avoid smoking uptake and support smoking cessation, as stopping smoking reduces the risk of dementia even in later life
- Provide all children with primary and secondary education
- Reduce obesity and the linked condition of diabetes
- Sustain midlife and possibly later-life physical activity
- Addressing other putative risk factors for dementia (e.g. sleep), through lifestyle interventions, will improve general health

Adapted from Livingston et al, *Lancet* 2020; 396:413-46 [103].

course (Box 3) [103]. Individually, cognitive benefits of discrete interventions such as a heart-healthy diet [66,115,118,119], appropriate control of diabetes [120–122] or intensive blood pressure control [123] are of key importance. However, evidence suggests that addressing multiple risk factors at once – multimodal intervention – is more efficacious than unimodal interventions [115, 124–126]. For example, recent results from two large longitudinal trials demonstrated that individuals in the mid- to late stages of life could lower their risk of AD by as much as 60% by adhering to 4 or all 5 of 5 prespecified healthy behaviours [127]. These healthy behaviours included weekly moderate or vigorous physical exercise, not smoking, light-to-moderate alcohol consumption, a brain-healthy diet and remaining cognitively engaged [127].

Regular evaluation of cognition is good clinical practice

A recent review from the US Preventive Services Task Force (USPSTF) notes that there is insufficient evidence available to determine the value of cognitive impairment screening in a meaningful way [128]. However, with very limited screening data available, and substantial challenges in designing and conducting randomized controlled trials about screening for and treating subsequently identified cognitive impairment, the absence of evidence should not be taken to mean

that screening has no benefits [94]. Furthermore, Alzheimer's Drug Discovery Foundation and others [94, 129] have correctly pointed out that the USPSTF uncovered no negative evidence related to screening, and it would be negligent to leverage the USPSTF report to support inaction, or to infer that people with memory or related cognitive problems should forgo assessment.

Consistent timely diagnosis of AD depends on healthcare providers' awareness of early signs and symptoms of cognitive impairment and their engagement in appropriate assessment [130]. What is feasible, however, may be somewhat practice-dependent, given variability in time, staff and resources. An immediate gain in detecting incipient cognitive-behavioural impairment will come from appropriately evaluating all patients who self-report a concern about cognition, behaviour or functioning; or for whom family or close relations identify such concerns; or in whom a clinician suspects such changes [74, 75]. Beyond that, clinicians should consider the value of screening for cognitive impairment in a medical context on an individualized, and patient- and family-centred basis [94]. Although Alzheimer's Association discourages one-time population-wide memory or dementia screening in nonmedical settings (e.g. at a health fair), the organization does distinguish routine cognitive assessments under a clinician's care from population-wide screening and

encourages such routine assessments [71]. The AAN also recommends, as a quality measure, an annual assessment of cognitive health in all patients 65 years and older seen in neurologic practice, and considers annual cognitive screenings in this population consistent with high-quality care, given that age itself is a significant risk factor for cognitive decline and MCI is increasingly prevalent with older age [131].

Routine assessment for cognitive-behavioural impairment is an essential element of good clinical practice. If such routine assessment is prohibitive for any practice, PCCs should consider prioritizing proactive, serial inquiry about signs and symptoms of AD in their patients who have known risk factors for dementia, such as cognitive complaints or family history of AD, advanced age, midlife hypertension, obesity or diabetes [70, 125, 132].

Use objective tools to monitor cognitive function proactively

This section briefly describes selected tools commonly used to evaluate for cognitive impairment in clinical practice. This is not an exhaustive list, and some instruments used by PCCs may not be described here – that should not necessarily discourage PCCs from continuing to use an established and preferred instrument. Most of the instruments we highlight are administered by a healthcare professional; others are informant-based or self-administered. Regarding the latter, it is important to note that as AD progresses, patients will experience anosognosia (i.e. lack of insight) or memory deficits, making self-reports less reliable.

Early signs and symptoms of cognitive-behavioural impairment due to AD often include subjective complaints and behavioural changes; work-related problems; the abandonment of hobbies or interests; trouble managing finances; difficulty remembering appointments, important dates or taking medications as prescribed; problems playing games of skill; challenges keeping track of current events; and difficulties with travel (e.g. public transportation) [133, 134]. Importantly, these difficulties may be reported more reliably by informants than by patients themselves. Current guidelines stress the importance of obtaining information from an informant [72], and incorporating informant-based questionnaires and prioritizing their use will lead to improved disease detection [135]. Alzheimer's Questionnaire (AQ) [136] and

the Ascertain Dementia 8-Item Informant Questionnaire (AD8) [137] are simple-to-administer, informant-based, time-efficient tools that aid in capturing incident cognitive decline (Table 2). Although slightly lengthier, another attractive option is the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). This 10- to 15-item questionnaire is completed by an informant and rates cognitive changes over time on a 5-point Likert scale [138].

Alzheimer's Association has issued recommendations for PCCs to help guide a direct, patient-focused cognitive function evaluation during annual wellness visits in Medicare beneficiaries [72]. These recommendations emphasize the use of structured assessments for routine evaluation of cognitive decline that may suggest AD [59, 72], as detection of cognitive impairment can be enhanced by specific questions about changes in memory, language and the ability to complete routine tasks. In fact, structured tools are more likely to detect even mild cognitive decline when compared with unaided detection [139]. In certain studies, the routine use of a brief cognitive assessment tool with all patients increased the detection and diagnosis of cognitive impairment or dementia by at least two- to threefold when compared with not using a validated assessment [140, 141]. Objective assessments can be successfully completed by several members of the multidisciplinary team, including nurses and physician assistants [140–142]. Thus, familiarity with at least one brief cognitive assessment developed for direct patient assessment is also important – particularly in follow-up to or in the absence of informant information [135].

The Mini-Mental Status Exam (MMSE) [143] is the most widely used and best-known short cognitive test, with an extensive empirical base related to it [144]. However, the MMSE has limited effectiveness for detecting MCI in its earlier stages and suffers from other limitations, such as a lack of standardization, strong susceptibility to socio-economic factors and a lack of suitability for illiterate individuals [144–146]. The MMSE is also subject to user fees secondary to copyright protection [144–146]. Other tools may have fewer limitations and may be as sensitive or even more sensitive for detecting earlier stages of clinical disease. These assessments include the Memory Impairment Screen (MIS) [147], the Montreal Cognitive Assessment (MOCA) [148], the Mini-Cog [149] and the St

Table 2 Recommended standardized tools for assessing for cognitive or functional impairment

	Tool	Brief description	Scoring and interpretation
INFORMANT-BASED ASSESSMENTS	Alzheimer's Questionnaire (AQ) [136,170,171]	<ul style="list-style-type: none"> Brief informant-based assessment 21 yes/no questions related to domains of memory, orientation, functional ability, visuospatial abilities and language Approximately 3 min to administer 	<ul style="list-style-type: none"> Score based upon number of 'yes' answers Range from 0 to 27 Normal: ≤ 4 Mild cognitive impairment: 5–14 Dementia: ≥ 15
	Ascertain Dementia 8-Item Informant Questionnaire (AD8) [137,172]	<ul style="list-style-type: none"> Brief informant-based questionnaire 8 yes/no questions designed to assess changes in the past few years in memory, orientation, executive functioning and/or interest in activities Approximately 3 min to complete 	<ul style="list-style-type: none"> Scores based upon number of 'yes' answers Range from 0 to 8 Normal: 0–1 Cognitive impairment likely: ≥ 2
PATIENT-BASED ASSESSMENTS	Memory Impairment Screen (MIS) 147173	<ul style="list-style-type: none"> 4-item delayed free- and cued-recall test of memory impairment Approximately 4 min to complete (plus a delayed recall section requiring delay of 5 min) 	<ul style="list-style-type: none"> Score based upon recalling each word 5 min later; 2 points for spontaneous recall and 1 point for cued recall Range from 0 to 8 MCI: ≤ 5 Dementia: ≤ 4
	Montreal Cognitive Assessment (MOCA) [148,174,175]	<ul style="list-style-type: none"> Screening tool assessing 8 cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual skills, calculations and orientation Approximately 10 min to complete 	<ul style="list-style-type: none"> Score based upon summing scores of correct answers Range from 0 to 30 Normal: ≥ 26 Mild cognitive impairment: 18–25 Moderate cognitive impairment: 10–17 Severe cognitive impairment: < 10
	Mini-Cog [149,176,177]	<ul style="list-style-type: none"> 2 components: 3-item recall test for memory and a simply scored clock drawing test Approximately 3 min to complete 	<ul style="list-style-type: none"> 5 total points possible; 1 point for each word remembered; and 2 points for a correctly drawn clock Lower likelihood of dementia with total score of 3–5
	St Louis University Mental Status (SLUMS) [150,178,179]	<ul style="list-style-type: none"> 11-question clinician-administered screening questionnaire that tests orientation, memory, attention and executive function Approximately 7 min to complete 	<ul style="list-style-type: none"> Total score: 1–30 Normal: 27–30 (high school education); 25–30 (less than high school education) MCI: 21–26 (high school education); 20–24 (less than high school education) Dementia: 1–20 (high school education); 1–19 (less than high school education)

Louis University Mental Status (SLUMS) Examination [150] (Table 2). Other potential tools of interest include the Self-Administered Gerocognitive Exam (SAGE) [151] and the Brief Interview for Mental Status (BIMS). The SAGE is a 10- to 15-minute self-administered test that assesses multiple areas of cognition. A SAGE score can be calculated quickly by any trained healthcare professional. The BIMS is a short performance-based cognitive screener expressly designed to facilitate cognitive screening in Minimum Data Set (MDS) assessments [152] and is required by CMS as part of current MDS evaluation for residents of skilled nursing facilities [152].

Monitor cognitive function and fully evaluate the patient when impairment is noted

Monitoring individuals at risk of cognitive impairment is the first step in increasing timely diagnosis. Our proposed evaluation 'pathway', provided here to help clinicians navigate a standard workup (Fig. 2), is unique in that, in the absence of a patient complaint, it recommends beginning such monitoring with a brief, self-administered, care partner-focused assessment of the patient's cognition/functioning before proceeding with a standard structured assessment of the patient's cognition/functioning. Of note, although the regular use of screening/assessment tools can improve the detection of cognitive impairment in its earliest stages [72], the scores on any assessment are not a diagnosis per se, and the score must be interpreted in the context of a comprehensive evaluation of the patient [153]. Conversely, a 'normal' score on a cognitive screening tool used by itself may not necessarily exclude subtle impairment nor substantial functional or behavioural problems.

Thus, regardless of the source of information on suspected MCI or mild AD dementia, clinicians should obtain a comprehensive medical history and perform an examination focusing on cognitive function, behaviour/neuropsychiatric status, ADLs, medications, medical comorbidities (including neurologic and/or psychiatric conditions) and laboratory testing (Fig. 2) [87, 154]. Neuropsychological evaluation can be considered to establish the extent and severity of a patient's cognitive impairment objectively, via standardized tests that assess cognitive domains of interest (i.e. memory, attention; processing speed; executive, language and visuospatial domains), and to track the progression of these parameters over time.

Patients who undergo this evaluation process should be monitored serially and subspecialty consultation should be considered (Fig. 2). The PCC, familiar with one or more brief assessments of cognition and function, should conduct serial assessment with the same instrument, preferably at intervals of at least 6 months to reduce practice effects artificially inflating test scores, and to determine whether the patient is declining, improving or staying the same. As previously noted, MCI can improve, remain stable or worsen over time, and any change in status has prognostic implications [81, 130, 155].

Although principles of good AD management are beyond the scope of this article, in general, patients with early AD should be counselled on nonpharmacologic interventions to mitigate further cognitive decline [81, 86, 131]. Patients should also be considered for pharmacologic therapy, particularly once DMTs become available [86, 87, 155]. Support agencies such as Alzheimer's Association, the National Council on Aging, Alzheimer's Foundation of America, Alzheimer's Disease Education and Referral Center, and others are vital resources for patients and their families. PCCs should refer patients to these agencies when appropriate. Referrals to memory research centres or directly to clinical trials through the National Institutes of Health (<https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/web-sites-information-about-clinical-trials>) or Alzheimer's Association Trial Match (<https://trialmatch.alz.org/>) remain critically important.

Current biomarkers can support AD identification and diagnosis

In general, biomarkers of disease can be used in multiple research or clinical settings, aiding in risk assessment, disease detection, prognosis, treatment selection and other functions (Appendix). Certain well-established biomarkers are currently used to characterize AD (Table 3). For the most part, these markers are used primarily in clinical research. Conversely, the use of AD biomarkers is limited in clinical practice; in fact, the most recent AAN MCI guidelines [81] do not recommend the routine use of AD biomarkers to diagnose AD, and A β PET scans are not routinely reimbursed in the United States. This scenario, however, is expected to change with the potential regulatory approval of a DMT. Since the majority of AD DMT clinical trials require that patients have the confirmed presence of AD pathologic changes (via A β PET or CSF), it is

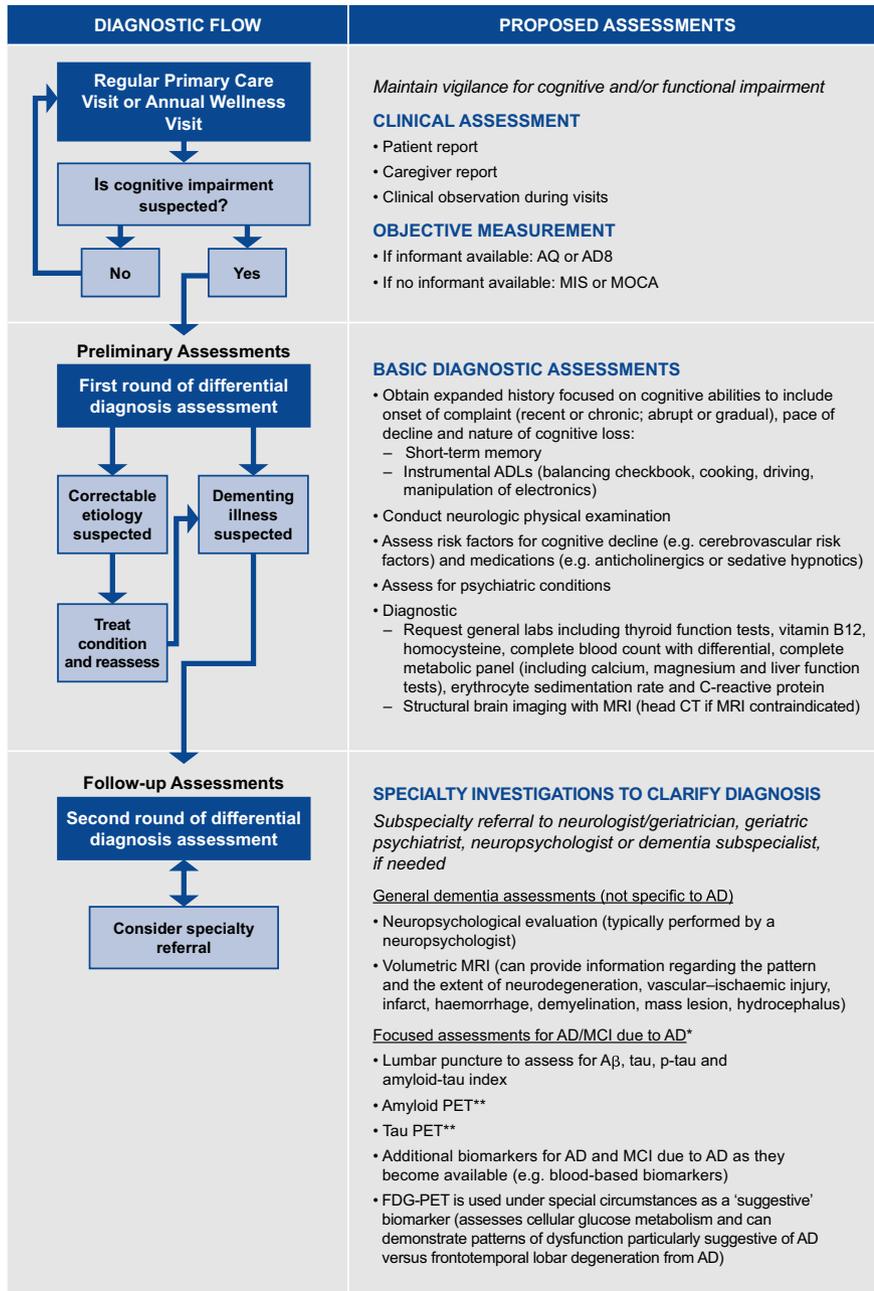


Fig. 2 A pathway for monitoring and evaluating individuals at risk of cognitive impairment. This pathway suggests a standard workup to evaluate cognitive impairment and also includes groupings of specific tests into those that are focused on detecting cognitive impairment/dementia due to AD versus those that are less specific but that still help identify a differential diagnosis for other causes of cognitive impairment/dementia. It is important to recognize that this decision tree does not offer staging for AD. As DMTs become available, staging will become more relevant, as these drugs will likely be FDA-indicated based on stage. A β , amyloid-beta; AD, Alzheimer’s disease; AD8, Ascertain Dementia 8-Item Informant Questionnaire; AQ, Alzheimer’s Questionnaire; CT, computed tomography; FDG, fluorodeoxyglucose; MCI, mild cognitive impairment; MIS, Memory Impairment Screen; MOCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; PET, positron emission tomography; TFT, thyroid function test

Table 3 Established biomarkers of AD

CSF biomarkers	
A β	<ul style="list-style-type: none"> • Diagnostic biomarker • Aβ plaque deposits are used widely to characterize AD [163] • CSF samples from patients with AD show a significant reduction in CSF Aβ (1-42) compared with samples from controls [163] • CSF Aβ changes do not correlate well with symptomatology [180,181]
Tau protein	<ul style="list-style-type: none"> • Tau protein, known to increase gradually with age, shows a significant increase in the CSF of patients with AD [163] – and is considered a biomarker of neurodegeneration
Phosphorylated tau	<ul style="list-style-type: none"> • Elevated levels of phosphorylated tau are observed in the CSF of patients with AD [163] • Correlation with clinical stage [182] – considered both a diagnostic and a staging/prognostic biomarker
Neuroimaging	
Amyloid PET*	<ul style="list-style-type: none"> • Diagnostic biomarker • Measures the amount of fibrillar Aβ in the brain [160] <ul style="list-style-type: none"> – To date, 3 compounds have been approved by the FDA for Aβ imaging (¹⁸F-florbetapir; ¹⁸F-flutemetamol; and ¹⁸F-florbetaben) [163,183] • Aβ PET imaging detects Aβ pathology early in the course of AD [160]
Tau PET*	<ul style="list-style-type: none"> • Measures the amount of fibrillar tau in the brain • To date, 1 compound has been approved by the FDA for tau imaging (¹⁸F-flortaucipir) [184]
FDG PET	<ul style="list-style-type: none"> • In patients with AD, areas of the brain exhibit hypometabolism indicative of reduced brain activity [185,186] • Predictive of future cognitive decline [185,186]
MRI	<ul style="list-style-type: none"> • Biomarkers include structural MRI measurements of brain volume and neuronal connectivity [160] • Changes in white and grey matter, hippocampus, amygdala, basal ganglia nuclei and ventricular volumes are highly sensitive to characteristic patterns of subregional atrophy and are promising tools to aid in early detection of neurodegeneration in patients with mild AD and MCI due to AD [187]

Abbreviations: A β , amyloid-beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; CMS, Centers for Medicare & Medicaid Services; FDA, Food and Drug Administration; FDG, fluorodeoxyglucose; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography.

*Although approved by the FDA, this imaging procedure is not yet reimbursed by CMS.

anticipated that confirmation of such underlying pathology will be a requirement for individuals to be eligible to receive DMTs, at least for those targeting A β . CSF biomarkers are generally cheaper to acquire than PET-based biomarkers. They require less advanced instrumentation and may be more readily available in clinical practice [156]. Amyloid PET scans offer the advantage of being less invasive [156], but do expose the patient to radiation.

Confirmation of an AD diagnosis via biomarkers may significantly impact the clinical management

of the disease. A recently reported national study (Imaging Dementia – Evidence for Amyloid Scanning [IDEAS]) found that providing clinicians with the brain A β PET scans of their cognitively impaired patients changed the way they managed these patients in nearly two-thirds of cases [157]. Specifically, there was increased prescribing of cholinesterase inhibitors and memantine after positive A β PET in participants with MCI. Furthermore, nearly half of all patients who had not been previously diagnosed with AD received a new diagnosis of AD following positive A β PET scans [157]. In contrast, based on a negative A β PET

scan, AD was ruled out in approximately 1 in 3 patients who had previously received an AD diagnosis [157]. Ongoing developments and anticipated innovations, particularly in BBBMs, will certainly modify future availability and coverage of biomarker assessments, ultimately enabling their widespread use in clinical care.

The ethical implications of disclosing biomarker results are complex. First, the sensitivity and specificity of some biomarkers may be currently inadequate for broad clinical use, and biomarkers are in general subject to false-negative and false-positive results. Moreover, at present, clinically classifying presymptomatic patients within the AD continuum is controversial, given both the absence of a DMT and the fact that elevated A β levels can be found in cognitively intact older adults, and not all of them will progress to dementia during their lifetime [29, 158], due to various factors, including resilience and censoring due to death.

Emerging biomarkers for AD will expand the clinical utility of these tools

Emerging research is anticipated to expand the utility of existing biomarkers in AD and introduce novel biomarkers that are not only less invasive, but that are also more sensitive, specific and cost-

effective (Table 4) [129, 159–161]. BBBMs in AD are of particular relevance in this discussion, as these are likely to expand beyond the offices of AD specialists. The development of BBBMs includes investigation into plasma A β , phosphorylated tau (p-tau), and neurofilament light species, as well as plasma-based levels of protein markers of circulatory microribonucleic acid, cholesterol metabolism, oxidative stress, coagulation and fibrinolysis, and inflammation [162–164]. For example, recent analyses suggest that plasma p-tau is increased across early and later stages of AD, is highly correlated with assessments based upon tau PET and CSF p-tau181, and can be used to differentiate AD dementia from non-AD neurodegeneration with an accuracy similar to other more invasive modalities of tau assessment [165]. In mid-2020, plasma p-tau217 was reported to discriminate AD from other neurodegenerative diseases with higher accuracy than established biomarkers such as MRI-based measures, and with performance similar to CSF- and PET-based measures [166]. These findings suggest a potential value of p-tau as a minimally invasive diagnostic biomarker, although further research is needed to validate these findings across populations, to optimize assessment assays and to determine the role of p-tau in clinical care. Plasma neurofilament light has also demonstrated reliability in detecting neurodegeneration

Table 4 Selected emerging biomarkers for AD

Biomarkers of A β and tau pathology

- Plasma A β ₄₂/A β ₄₀ (biomarker for A β pathology) [188]
- Plasma p-tau [189]
- BACE1 in CSF; β -secretase enzyme involved in cleaving amyloid precursor protein; may be elevated in earliest stages of AD [190]

Biomarkers for neurodegeneration

- Neurofilament light (NFL) in CSF or in plasma
 - Structural protein present in long axons [191]
 - Concentration of NFL is increased in AD patients, particularly those with rapid disease progression [191]
 - May reflect subcortical/white matter damage across a range of neurodegenerative/neuroinflammatory and infectious diseases, including AD [190]
- Neurogranin (Ng; NRG1) in CSF
 - Dendritic protein enriched in neurons that is involved in long-term potentiation of synapses [191]
 - CSF concentration of Ng is increased in AD but not in other neurodegenerative disorders [191]

Novel neuroimaging biomarkers

- Synaptic vesicle protein 2A (SV2A) PET, a marker of synaptic density [192]
- Translocator protein (TSPO) ligand PET, a marker of neuroinflammation [193].

Abbreviations: A β , amyloid-beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; p-tau, phosphorylated tau.

and neuronal injury, irrespective of the aetiology, and may play a diagnostic role [167, 168].

Summary

The mantra ‘time lost is brain lost’ is often used to emphasize the need for a rapid response during a neurologic emergency, such as stroke. It is becoming increasingly clear that this adage should be applied to the AD continuum to encourage patients and family members to recognize the signs and symptoms of emerging cognitive decline, and to motivate clinicians to intervene whilst patients are cognitively intact or are only minimally impaired. We are approaching a time when simple and accessible diagnostic tools that allow for detection of AD in its earlier stages will be more widely available, and when DMTs will provide an intervention that may alter disease trajectory. The introduction of these clinical tools will further lead to an evolution in already-dynamic best practices, and it is foreseeable that these advances may drive some elements of AD care into the purview of subspecialists.

However, if clinicians or healthcare providers are to meet the goal of consistently diagnosing AD in a timely fashion, their vigilance for this disease must increase, and this may require a foundational shift in clinical practice, including primary care. The role of the PCC in the care of diseases of cognitive impairment is becoming ever more important. PCCs can feel encouraged by recent studies that demonstrate the benefits of their hard work. Multimodal interventions focused on reduction in cardiovascular and other risks have reduced the incidence of dementia in the United States and Europe over the past one or two decades. Unfortunately, given the demographics of the ‘silver tsunami’, the prevalence of dementia is rapidly increasing [107–110]. It is therefore critical to continue to encourage multimodal interventions that include a healthy diet, physical exercise, mental and social stimulation, and control of comorbidities.

Timely and accurate diagnosis and concomitant application of multimodal intervention that eventually includes a DMT may slow or delay cognitive decline due to AD, at a point in the disease continuum where (i) neurodegeneration is not so sufficiently advanced as to render intervention biologically ineffective; and (ii) a patient’s independence and quality of life are relatively robust and

subsequently defended. Timely and accurate diagnosis of early AD will depend on multiple evolving parameters related to detection, evaluation and biomarker-aided assessments that we expect to expand presently, both in accessibility and in ease of use. Along with continuing general preventative efforts, the detection of early disease offers the best opportunity for counselling, lifestyle modification and medical intervention – as well as long-term planning and participation in research. We look forward to rapid refinements in healthcare that will enable all providers, including primary care clinicians, to fully reimagine their approach to the AD disease spectrum, leading to better patient outcomes.

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APPENDIX

Types and representative examples of biomarkers

A **biomarker** is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes or responses to an exposure or intervention [205]. A list of commonly recognized types of biomarkers can be found below.

- **Susceptibility or risk** biomarkers indicate the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition. An example of a risk biomarker is the use of C-reactive protein levels to identify adult patients with a greater likelihood of incident coronary disease.
- **Predictive** biomarkers identify individuals who are more likely than similar individuals without the biomarker to experience a favourable or unfavourable effect from exposure to a medical

product or an environmental agent. For example, certain cystic fibrosis transmembrane conductance regulator mutations may be used in clinical trials as predictive biomarkers to identify patients more likely to respond to particular treatments.

- **Prognostic** biomarkers are used to identify the likelihood of a clinical event, disease recurrence or progression in patients who have a particular disease or medical condition; for example, increasing prostate-specific antigen may be used to assess the likelihood of cancer progression when evaluating patients with prostate cancer during follow-up.
- **Monitoring** biomarkers are measured serially to assess the status of a disease or medical condition for evidence of exposure to or the effect of a medical product or environmental agent. For example, the HCV-RNA level may be used to assess treatment response in patients with chronic hepatitis C, whilst international normalized ratio or prothrombin time may be used to assess whether the desired effect of anticoagulation has been attained in patients who have been prescribed warfarin.
- **Diagnostic** biomarkers are used to detect or confirm the presence of a disease or condition, or to identify individuals with a subtype of the disease, such as using blood sugar (or HbA1C) to identify patients with type 2 diabetes, or repeated blood pressure reading to identify those with essential hypertension.
- **Pharmacodynamic/response** biomarkers are used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent. Common examples include the use of blood pressure readings to assess response to an antihypertensive agent, serum LDL cholesterol to assess response to a lipid-lowering agent or dietary change, or viral load to evaluate response to antiretroviral treatment.■